REMARKS

Claims 1-31 are pending in the application. Claims 1-15 are examined. Non-elected and non-examined claims 16-31 are canceled herein without prejudice to the filing of divisional or other continuing applications thereon.

An Information Disclosure Statement is submitted with the present Response. It is respectfully requested that the Examiner review these references and make them of record in accordance with 37 C.F.R. § 1.56 and M.P.E.P. § 609.

I. Disclosure of Actions in Related Applications

Applicant would like to draw the Examiner's attention to the restriction requirement mailed on June 7, 2007, in application no. 10/752,515, attorney docket no. 9626-17IP (pancreatitis) (no longer pending), which is a continuation-in-part of the present application.

Applicant would also like to draw the Examiner's attention to the restriction requirement mailed June 7, 2007, response mailed October 15, 2007, and non-final office action mailed October 31, 2007, in application no. 10/753,957, attorney docket no. 9626-17IP2 (pancreatitis) (pending), which is a continuation-in-part of the present application.

Applicant also would like to draw the Examiner's attention to:

- the restriction requirement mailed on June 11, 2007, in application no. 10/752,522, attorney docket no. 9626-18 (neuroleptic malignant syndrome) (no longer pending);
- the restriction requirement mailed on June 14, 2007, the response mailed July 20, 2007, the non-final office action mailed October 2, 2007, and the response mailed January 14, 2008, in application no. 10/753,958, attorney docket no. 9626-19 (neuroleptic malignant syndrome) (pending);
- the restriction requirement mailed June 11, 1007, in application no. 10/752,523, attorney docket no. 9626-20 (rhabdomyolysis) (no longer pending);
- the restriction requirement mailed June 14, 2007, the response mailed July 20, 2007, the non-final office action mailed October 2, 2007, and the response mailed January 14, 2008, in application no. 10/753,955, attorney docket no. 9626-21

(rhabdomyolysis) (pending);

- the restriction requirement mailed June 11, 2007, in application no. 10/752,516, attorney docket no. 9626-22 (hyperammonemia) (no longer pending);
- the restriction requirement mailed June 14, 2007, and response mailed November 29, 2007, in application no. 10/753,956, attorney docket no. 9626-23 (hyperammonemia) (pending);
- the non-final rejection mailed June 14, 2007, and response mailed December 14, 2007, in application no. 10/784,145, attorney docket no. 9626-24 (MGUS, SMM, MM) (pending).

II. Rejection under 35 U.S.C. § 103

Claims 1-15 are rejected under 35 U.S.C. § 103(a) as obvious over Elan Pharma, Zonisamide FDA Approved Labeling Text (March 27, 2000) in view of Iliopoulou et al, "Acute Pancreatitis Due to Captopril Treatment," *Digestive Diseases and Sciences*, 46(9):1882-1883 (September 2001). This rejection is respectfully traversed.

As stated in the recently published Examination Guidelines for Determining Obviousness, "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co*...." (Examination Guidelines for Determining Obviousness Under 35 U.S.C 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* Federal Register Vol. 72, No. 195, 57526-57535, 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143). First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir.

1991). Finally, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both come from the prior art, not from the Applicant's disclosure. *See In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); M.P.E.P. § 2143.

As noted in the Office Action on Page 4, Elan does not teach informing the patient that pancreatitis is a potential side effect of zonisamide treatment. At pages 16-19, Elan teaches:

- about 34 side effects occurring in at least 2% of patients treated with zonisamide;
- about 13 sides effects occurring in at least 1% of patients treated with zonisamide;
- about 82 side effects occurring in 1% to 0.1% of patients treated with zonisamide; and
- about 42 side effects occurring in less than 0.1% of patients treated with zonisamide.

Elan does not provide any relationship or link between any of the 171 possible side effects described therein with any of the 6 claimed symptoms associated with the adverse event of pancreatitis.

One cannot simply pick and choose among the individual elements of assorted prior art references to re-create the claimed invention. Rather, "some teaching or suggestion in the references to support their use in the particular claimed combination" is needed. *Symbol Technologies, Inc. v. Opticon, Inc.* 935 F.2d 1569, 1576 (Fed. Cir. 1991). There is no motivation found for one skilled in the art to specifically select the 6 claimed symptoms out of the 171 symptoms described by Elan to conclude that pancreatitis is a possible adverse event of zonisamide treatment.

Iliopoulou does not cure the deficiencies of Elan.

Iliopoulou is a case study on captopril (an ACE inhibitor) causing acute pancreatitis. The chemical structure of captopril is unrelated to the chemical structure of zonisamide.

In one sentence, Iliopoulou states:

> It is reported that the most frequently incriminated drugs [causing acute pancreatitis] are sulfonamide derivatives, valproic acid, nonsteroidal

> antinflammatory drugs, estrogens, L-asparaginase, salicylates, thiazide diuretics, and vinca alkaloids.

This list encompasses an extraordinary number of drugs, such that one skilled in the art would not be apprised of which individual drugs contained within this broad listing would be associated with an adverse event of pancreatitis. Applicant therefore respectfully asserts that there is no teaching or suggestion in Iliopoulou that zonisamide, in particular, may cause pancreatitis.

To the extent that Iliopoulou identifies sulfonamide derivatives, one skilled in the art would appreciate that the chemical arts are unpredictable and that not every sulfonamide derivative will result in the side effect of pancreatitis.

In fact, Frick et al., the reference cited in the Iliopoulou article after the broad statement quoted above, states: "It is concluded that for none of the drugs studied the available data are consistent enough to support a definite association with acute pancreatitis." ("Drug induced acute pancreatitis: Further criticism," Dig. Dis. 11(2):113-132 (1993), Abstract, emphasis added). This statement in Frick et al. argues against a generalized association of pancreatitis with a certain class of drugs, particularly sulfonamides, for which the data were described as "weak" by Frick et al. (Abstract).

In addition, a later article on this topic co-authored by Dr. Frick, Wilmunk et al., "Drug-Induced Pancreatitis," Drug Safety 14(6):406-423 (1996), states:

> Sulphonamide medication has been associated with acute pancreatitis in 4 case reports. In 2 patients treated with cotrimoxazole (trimethoprim-sulfamethoxazole), the evidence was anecdotal. In a third patient with concurrent sterile meningitis, symptoms of acute pancreatitis weakly returned upon rechallenge. In the fourth patient, evidence was based on controlled rechallenge, although the patient had had a renal transplant and was concurrently treated with azathiprine, corticosteroids and furosemide.
>
> The association between acute pancreatitis and sulphonamides is not strong.

(page 413, second column, fourth full paragraph, citations omitted, emphasis added).

As further evidence of the state of the art at the time of filing of the present application, the *Nursing 2002 Drug Handbook* 683 (22nd ed. 2002), lists various "sulfonamides" in its subchapter of "anti-infective drugs" on pages 130-136: co-trimoxazole, sulfadiazine,

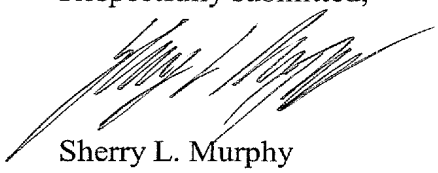
sulfamethoxazole, sulfisoxazole and sulfisoxazole acetyl. Significantly, pancreatitis is listed as an adverse reaction under some, but not all, of these sulfonamides. Pancreatitis is listed as an adverse reaction in co-trimoxazole (pages 130-131) and sulfamethoxazole (pages 133-134), but not in sulfadiazine (pages 132-133), sulfisoxazole and sulfisoxazole acetyl (pages 135-136). Zonisamide, described in the subchapter on "anticonvulsants" of "central nervous system drugs" (pages 435-436), also does not list pancreatitis as an adverse reaction. This reference clearly indicates that not all sulfonamides were considered to carry a risk of pancreatitis in the art at the time of filing.

Given the state of the art at the time of filing as evidenced by the articles discussed above, Applicant submits that one of skill in the art would not have been motivated to inform a patient that pancreatitis is a potential side effect of zonisamide. In view thereof, Applicant respectfully requests that the rejection of claims 1-15 under 35 U.S.C. § 103(a) as obvious over Elan Pharma in view of Iliopoulou et al., be withdrawn.

III. Conclusion

In light of the foregoing, Applicant respectfully asserts that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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